UCRL-JC-122951 Abs

DELETION AND INSERTION SOMATIC MUTATIONS IN THE HYPOXANTHINE PHOSPHORIBOSYLTRANSFERASE GENE OF HEALTHY PEOPLE. K. J. Burkhart-Schultz snd I.M. Jones, Lawrence Livermore National Laboratory, Livermore, CA 94551

Deletion and insertion mutations are a major component of the mutation spectrum in the hypoxanthine phosphoribosyltransferase (hprt) gene of lymphocytes in healthy people. In a population of 172 people with an average age of 34 years and mutant frequency of 10.3 $x10^{-6}$, deletion and insertion mutations constituted 41% (89) of the 217 independent mutations. The remaining 59% were base substitutions. Mutations were identified by the hprt multiplex PCR assay of genomic DNA for the presence of exon regions (Gibbs et al.,1990) or by the sequencing cDNA and/or genomic DNA. The deletion and insertion mutations are divided about equally between +/- 1 to 2 basepair (bp) frameshifts (13%, 30), small deletions of 3-200 bp (12%, 26), and deletions of one or more exons (12%, 27). The remaining mutations were complex events (2%, 4) and tandem duplications (1%, 2; both in exon 6). The frameshift mutations were dominated by -1 bp deletions (21 of 30) and were in exon 3 more often than expected based on exon size (16 of 30; p=0.003). Four -1 bp and one +1 bp frameshifts were in the run of 6 Gs in exon 3 which was the only site in this study showing repeated mutation. Few frameshift mutations were at positions where base substitution mutations were detected. Strand slippage during replication may have been the mechanism for the creation of some mutations, but not all. Interestingly, more small deletions (8 of 26) occurred in exon 2 than in the other exons. The large deletions included 6 mutants with total hprt gene loss, 4 with exons 2+3 deleted, 9 others with multiple exons missing, and 8 with a single exon missing. The great diversity of deletion and insertion mutations in the hprt gene indicates that a wide range of mechanisms, operating at many different sequences produced the mutations. This broad deletion and insertion mutation spectrum provides a rich resource for examination of mechanisms of mutation. Work performed under the auspices of US DOE by LLNL under contract W-7405-ENG-48 with support from IA Y01-ES-80171 from NIEHS.